DOCKET No.: CP247 (CEPF-0006) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Olivier NECKEBROCK, et al.

U.S. Serial No.: 10/539,918 **Group Art Unit:** not yet known

International Application No.: PCT/FR2003/003799 **Examiner:** not yet assigned

International Filing Date: 18 December 2003

For: PROCESS FOR THE PREPARATION OF AND CRYSTALLINE FORMS OF OPTICAL ENANTIOMERS OF MODAFINIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ERWIN BLOMSMA, PH.D.

I, Erwin Blomsma, Ph.D. hereby declare the following:

(1) I, Erwin Blomsma, Ph.D. received a Master in Engineering in Chemistry and Biochemistry in 1991, and my Ph.D. in Applied Biological Sciences in 1995 from Katholieke Universiteit Leuven, Belgium. I presently serve in a consulting capacity as Strategic Development Officer for Avantium Technologies, Zekeringstraat 29, 1014BV, Amsterdam, The Netherlands. From 2000 to 2005, I served as Vice President of Technology for Crystallics B.V. and Avantium Life Sciences, and later as COO of Avantium Technologies. The experiments discussed below were performed under my direction and control. A copy of my resume is attached hereto as Exhibit 1.

(2) MODAFINIL is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. (PA, USA). It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) In 2003, at Cephalon's request, we performed high-throughput screening for MODAFINIL polymorphs under a variety of different crystallization conditions. As part of this work, we performed recrystallizations of the (-) enantiomer from ethanol, followed by high-throughput X-ray powder diffraction (XRPD) analysis and classification of the crystalline forms produced. The methods used to perform these experiments are reported in Exhibit 2.

(4) The results of the our ethanol recrystallizations are reported in the table attached hereto as Exhibit 3. Three distinct polymorphic forms of (-)-MODAFINIL, which we designated as Form A (-)-MODAFINIL, Form B (-)-MODAFINIL and Form C (-)-MODAFINIL, were obtained from the recrystallizations from ethanol that we performed. In one instance, a mixture of Form A and Form C was obtained. In other instances, the scattering intensity of the product was too low to identify what solid form was produced (designated "n" in Exhibit 3). The XRPD patterns and DSC thermograms of Form A (-)-MODAFINIL and Form B (-)-MODAFINIL Form C (-)-MODAFINIL are shown in Exhibit 4.

(5) On the basis of the results obtained in these experiments, I conclude that recrystallization of (-)-MODAFINIL under varying conditions from ethanol can result in production of more than one crystalline form of the compound. In my experience, and based upon the data herein, recrystallization from ethanol can result in three different polymorphic forms, or a mixture of polymorphic forms, depending upon the conditions under which the recrystallization is performed.

(6) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 1st 2006

Erwin Blomsma, Ph.D.

EXHIBIT 1

Erwin Blomsma
Karrestraat 88, 3020 Herent, Belgium - T/F +32 16 201368 - Mobile +32 473 673550

Date of birth: February 29th, 1968
Nationality: Dutch

WORK EXPERIENCE

2005- present **Avantium Technologies, *Strategic Development Officer***

Leading and directing Asian business development and operations.

Strategic advisor to Avantium management team.

Analysis and commercialization of Avantium IP.

Working as consultant through own company registered in Belgium. Advisor to other companies (Carver Europe, Mettler Toledo).

2004- 2005 **Avantium Technologies, *Chief Operating Officer***

Member of the executive management team of Avantium Technologies, a contract research company specialised in rational approaches to high-throughput experimentation.

Leading and directing operations of all R&D teams in chemicals & life sciences.

2000-2004 **Avantium Technologies, *Vice President Technology***

VP Technology of Crystallics and Avantium Life Sciences. Member of the management team of Avantium Technologies. Co-founder of Crystallics.

Active role in technology development, project management and scientific collaborations.

Invited speaker and sponsor of several conferences and symposia in the domain of solid-state research and chemical & process development.

1996-2000 **Janssen Pharmaceutica NV (Johnson & Johnson),**
Manager Chemical Process Technology

Manager of the chemical process technology group and member of the international engineering management team.

Responsible for the identification, selection and implementation of new process technologies for the worldwide chemical production facilities of Janssen Pharmaceutica (Johnson & Johnson). Focus on process analytical techniques for process monitoring and control (e.g. implementation of FTIR technology for end-point detection in catalytic hydrogenation reactions, implementation of FBRM technology for in-situ particle size analysis, etc).

Played a leading role in defining and setting up a company wide knowledge management and communication system based on Lotus Notes in which proprietary and commercial knowledge bases were later integrated.

Successfully launched an ambitious project to manage the lifecycle of a pharmaceutical process from process development through scale-up and engineering to process validation in the production facilities using knowledge management and simulation tools.

EDUCATION

1995-1996 **KU Leuven / UCB Fine Chemicals, *Post Doctoral*** **Belgium**

Short but successful post-doctoral study on the catalytic synthesis (objective to convert a batch process to operate in continuous mode) of amine derivatives for UCB Chemicals, Belgium.

1991-1995 **KU Leuven / Shell Research KSLA,**
PhD in Applied Biological Sciences (*) **Belgium/Netherlands**

PhD thesis within the frame of a research agreement between the Shell Laboratories in Amsterdam and the centre for surface science and catalysis at Leuven University (Prof. Dr. Ir. Jacobs).

Experience was gained through the design and construction of a fully automated microreactor-setup (gas phase) including hardware and software development, data analysis and visualisation techniques.

The experimental program yielded insight in the reaction mechanisms of alkane activation and isomerization pathways and was used to design novel catalytic systems (*de novo* design). The project yielded 2 patents on bimetallic bifunctional catalysts.

(*) The centre for surface science and catalysis is part of the faculty of agricultural sciences

1986-1991 **KU Leuven,**
Master in Engineering in Chemistry and Biochemistry **Belgium**

Specialisation in surface chemistry and food science & technology.

Engineering thesis on the catalytic partial oxidation of methane to synthesis gas, including the design, construction and set-up of an automated reactor system with on-line GC analysis. The experimental work covered the oxidative reforming of methane, carbon dioxide and steam reforming, etc. Graduated with distinction.

OTHER EXPERIENCES AND SKILLS

Professional training:

- Process Excellence / 6 sigma (Black Belt)
- Problem solving and Decision making (Kepner Tregoe)
- Project management
- Process safety (including HAZOP, SWIFT, PHA/PHR)
- Simulation and modelling (BatchCAD, Aspen Engineering Suite, etcetera)
- Knowledge management
- Automation (DCS/PLC/Proprietary systems)
- Process analytical techniques (in situ monitoring and control)
- Process technology (unit operations: crystallisation, solid-liquid separation, drying)
- Several courses followed and workshops given on Polymorphism and crystallisation

Publications:

- 1 publication on partial oxidation of methane to synthesis gas (> 80 citations)
- 6 publications and 2 catalyst patents on "alkane hydroisomerization and hydrocracking"
- > 4 patents or patent applications in the domain of solid state research
- > 50 lectures on Solid State Research and Combinatorial Chemistry / R&D

EXHIBIT 2

Experimental conditions:

Approximately 7 grams of the (-) enantiomer of MODAFINIL was delivered to us in two batches as a white powder.

The crystallization experiments were carried out in stainless steel (316L) well plates. The plates contain 96 individually sealed wells of 50 µL total volume. Two of the wells in each plate utilized ethanol as the solvent. From room temperature, the plates were heated to an initial temperature of 60 or 80 °C at a rate of 4.8 °C/min and, after 30 minutes, cooled at a slow (0.6 °C/min), medium (2 °C/min) or fast (300 °C/min, maximum setting) rate to a final T of 3 °C and kept at that temperature for a minimum of 1 h or a maximum of 48 h.

After crystallization and solvent evaporation (N_2 atmosphere), the crystalline products were harvested onto a special X-ray transparent carrier. Analysis was carried out with Crystallics' T2 high throughput XRPD set-up. The plates were mounted on a Bruker GADDS diffractometer equipped with a Hi-Star area detector. The data collection was carried out at room temperature using the monochromated CuK_α radiation in the region of 2θ between 3 and 42°. The diffraction pattern for each well was collected in two 2θ ranges ($3 \leq 2\theta \leq 21°$ for the 1st frame, and $19 \leq 2\theta \leq 42°$ for the second frame) with an exposure time of between 50 and 250 seconds for each frame.

After identification of the various solid forms, thermal analysis was used for further characterization whenever enough sample was available. Melting properties were determined from differential scanning calorimetry (DSC) thermograms recorded with a DSC822e (Mettler-Toledo GmbH, Schwerzenbach, Switzerland). The DSC822e was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; ΔH_f = 28.45 $J.g^{-1}$). Samples were sealed in standard 40 µL aluminium pans and heated in the DSC from 25 to 300°C with a heating rate of 20.0°C min^{-1}. Dry N_2 gas was used to purge the DSC equipment during measurement at a flow rate of 50 mL min^{-1}.

Mass loss due to solvent or water excretion from the crystals was determined by thermogravimetric analysis (TGA). During heating of a sample in a TGA/SDTA851e (Mettler-Toledo GmbH, Schwerzenbach, Switzerland) the weight of the sample was monitored resulting in a weight vs. temperature curve. The TGA/SDTA851e was calibrated for temperature with indium and aluminum. Samples were weighed in 70 µL alumina crucibles

and heated in the TGA from 25 to 300°C with a heating rate of 20°C min^{-1}. Dry N_2 gas was used for purging.

Digital images of the various solid forms were made using a Leica MZ9.5 stereomicroscope equipped with a Leica DC 300 digital camera.

Crystal Structure Determination

Single crystals of distinct phases identified by XRPD on the various 96-well plates were selected for full structure determination. For this, crystals were individually glued to a glass fibre, which was mounted on the X-ray diffraction goniometer. X-ray diffraction data was collected for some of these crystals at a temperature of 233 K using a KappaCCD system and Mo*K*alpha radiation generated by a FR590 X-ray generator (Bruker Nonius, Delft, The Netherlands). Unit-cell parameters and crystal structures were determined and refined using the software package maXus (Mackay *et al.*, 1997).

From the crystal structure the theoretical X-ray powder diffraction pattern was calculated using PowderCell for Windows version 2.3 (Kraus *et al.*, 1999).

Scale-Up Example:

Crystallics' Minimax parallel reactor set-up was used to conduct a series of larger scale crystallizations (in 1 mL glass vials), applying conditions selected from the polymorph screening experiments. These conditions are outlined in the results table. The Minimax reactor assembly is precision controlled and allows the precise measurement of temperature and turbidity of the crystallization solution throughout the experiment. For the experiment reported as Example 25 in Exhibit 3, 50 mg of MODAFINIL product was suspended in 333.33 µl ethanol to give a 7.5% w/v ratio. With 500 rpm continuous stirring, the crystallization mixture was heated from room temperature to 80 °C (Tmax) at 3°C/min, kept at this temperature for 30 minutes, and then cooled at 0.6 °C/min to 3 °C. The mixture was then kept at 3 °C for one hour prior to crystal structure determination.

EXHIBIT 3

Ex. No.	Heating rate (° C/min)	$T_{initial}$ (° C)	Hold (min)	Cooling rate (° C/min)	T_{final} (° C)	Hold (hour)	Modafinil Conc.	Solid Form Obtained
1	4.8	80	30	0.6	3	48	7.5%	A
2	4.8	80	30	0.6	3	48	15%	A
3	4.8	80	30	0.6	3	1	7.5%	C
4	4.8	80	30	0.6	3	1	15%	A
5	4.8	80	30	2	3	1	7.5%	A
6	4.8	80	30	2	3	1	15%	A
7	4.8	80	30	2	3	48	7.5%	A
8	4.8	80	30	2	3	48	15%	A
9	4.8	80	30	300	3	48	7.5%	B
10	4.8	80	30	300	3	48	15%	A
11	4.8	80	30	300	3	1	7.5%	A/C mixture
12	4.8	80	30	300	3	1	15%	A
13	4.8	60	30	0.6	3	48	7.5%	n
14	4.8	60	30	0.6	3	48	15%	A
15	4.8	60	30	2	3	48	7.5%	A
16	4.8	60	30	2	3	48	15%	A
17	4.8	60	30	300	3	1	7.5%	n
18	4.8	60	30	300	3	1	15%	A
19	4.8	60	30	300	3	48	7.5%	n

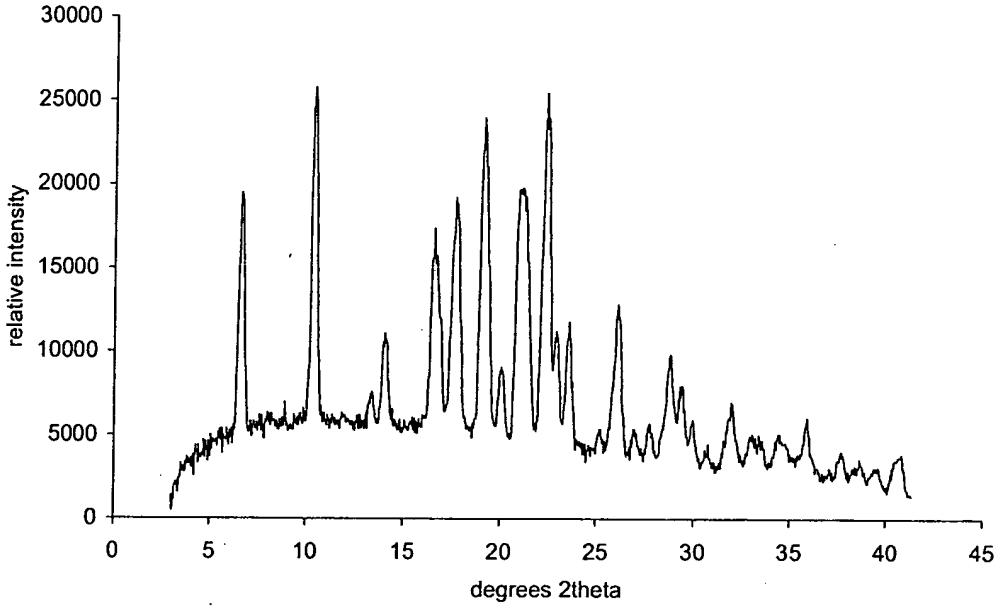
Ex. No.	Heating rate (° C/min)	$T_{initial}$ (° C)	Hold (min)	Cooling rate (° C/min)	T_{final} (° C)	Hold (hour)	Modafinil Conc.	Solid Form Obtained
20	4.8	60	30	300	3	48	15%	A
21	4.8	60	30	0.6	3	1	7.5%	n
22	4.8	60	30	0.6	3	1	15%	A
23	4.8	60	30	2	3	1	7.5%	A
24	4.8	60	30	2	3	1	15%	A
25*	4.8	80	30	0.6	3	1	7.5%	A

7.5% = 1.875 mg (-)-modafinil dissolved in 25 µl ethanol
15% = 3.75 mg (-)-modafinil dissolved in in 25 µl ethanol
Ex. No. 25* = 50 mg (-)-modafinil dissolved in 333.33 µl ethanol
n = scattering intensity of products too low to identify the solid form.

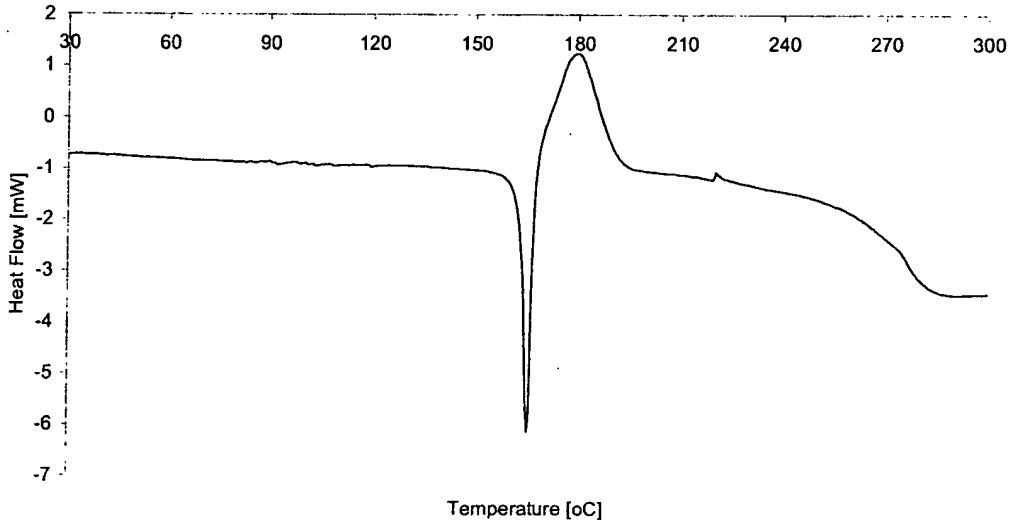
EXHIBIT 4

Crystalline Form A of (-)-MODAFINIL

XRPD

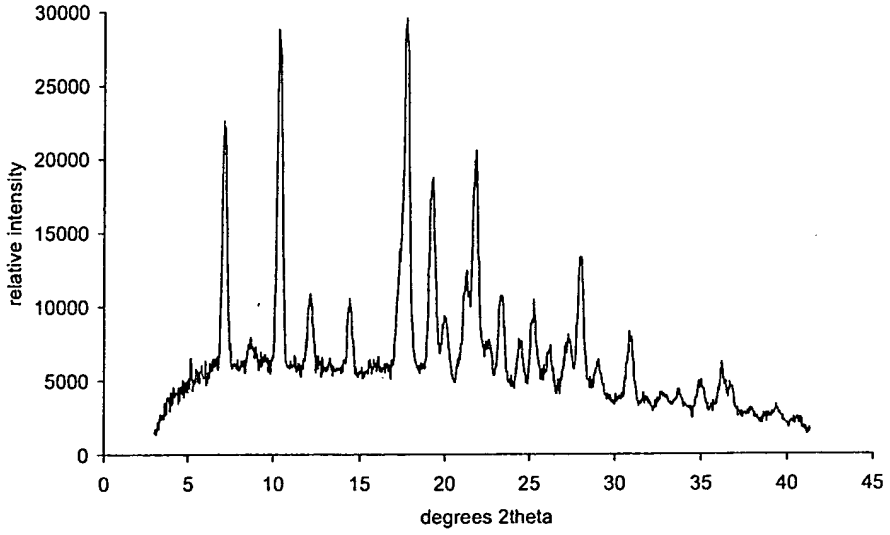


DSC

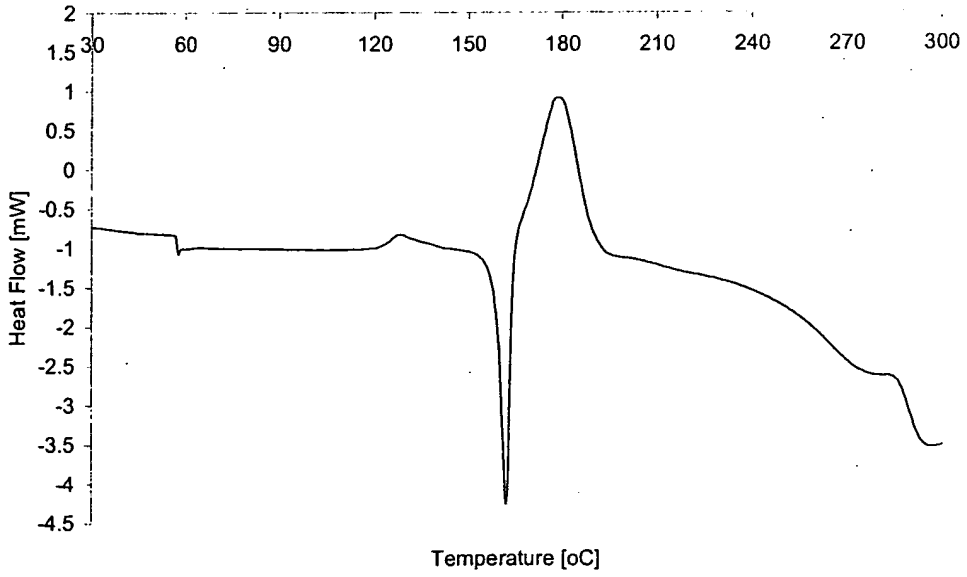


Crystalline Form B of (-)-MODAFINIL

XRPD

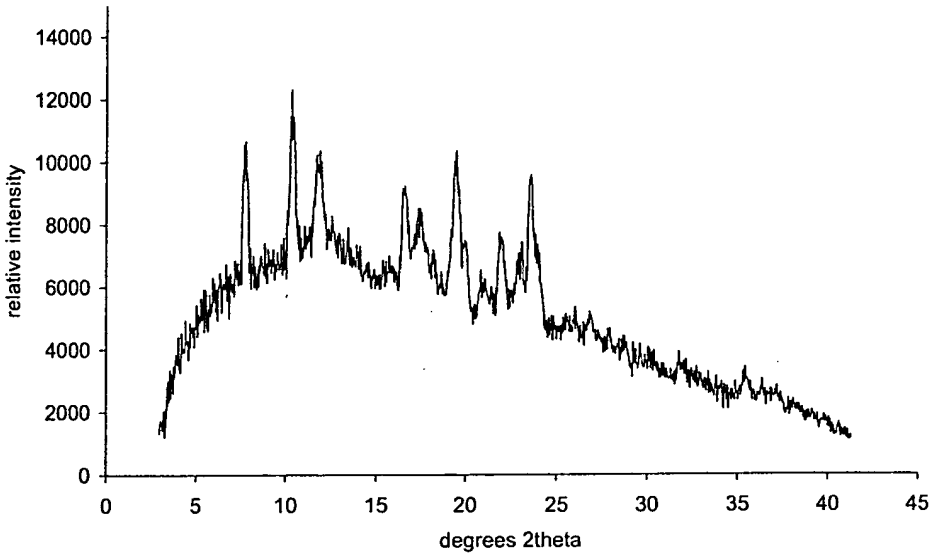


DSC



Crystalline Form C of (-)-MODAFINIL

XRPD



DSC